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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,954	06/21/2001	Maureen J. Charron	96700/667	6743

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EXAMINER	
NICKOL, GARY B	
ART UNIT	PAPER NUMBER
1642	6

DATE MAILED: 01/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,954	CHARRON ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *24-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Election filed November 1, 2002 (Paper No. 5) in response to the Office Action of October 03, 2002 is acknowledged and has been entered.

Claims 1-35 are pending in the application.

Claims 24-35 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 1-23 are currently under prosecution

Applicant's election with traverse of Group II, claims 1-7, 11-17, and 21-23 in Paper No. 5 is acknowledged. The traversal is on the ground(s) that the inventions of Groups I and II encompass the same inventions and that a search for one Group would necessarily identify art pertinent to the other group. Thus, applicants maintain that it would not place an undue burden on the Examiner to examine both Groups I and II. This argument has been considered and is found persuasive. Thus, Groups I and II have been joined.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration appears to be defective because it does not identify priority to the related US Application No. 09/516,214 filed March 1, 2000.

Claim Objections

Claim 21 is objected to for reciting, "the subject's prognosis worsens with an increase in GLUTx expression" followed by the very similar prognosis wherein "the subject's prognosis is unfavorable at high levels of GLUTx expression". These steps are objected to because there does not appear to be any measurable or quantitative distinction between evaluating a worsening prognosis or unfavorable prognosis since both steps are correlated with increases or high levels of GLUTx.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of assessing the prognosis of a subject who has cancer (i.e., adenocarcinoma) or a pre-neoplastic legion comprising assaying a diagnostic sample of the subject for GLUTx expression wherein:

1) the subject's prognosis improves with a decrease in GLUTx expression

2) the subject's prognosis worsens with an increase in GLUTx expression

3) the subject's prognosis is favorable at normal levels of GLUTx expression

4) the subject's prognosis is unfavorable at high levels of GLUTx expression

The claims are not enabled because the specification provides insufficient guidance and or objective evidence that the claimed method would reasonably provide a predictable *prognosis* for a subject who has cancer.

The specification teaches (page 15-16) that a correlation exists between tumor burden and the survival of a patient who has cancer. In the case of GLUTx, protein levels in non-metastatic rat mammary adenocarcinoma cells were significantly lower than those detected in metastatic rat mammary adenocarinoma cells. Thus, the specification asserts that overexpression of GLUTx correlates with the staging of the neoplastic lesion and the prognosis of the patient.

However, there is insufficient guidance and objective evidence to successfully use the method in order to predictably evaluate GLUTx for its prognostic ability in a subject with cancer. In particular, applicants have solely relied on the results from *in-vitro* data in order to characterize GLUTx as a predictor of patient outcome. Those of skill in the art recognize that *in-vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs; however, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment

as compared to the very narrowly defined and controlled conditions of an *in-vitro* assay does not permit a single extrapolation of *in-vitro* assays to a human patients' outcome or prognosis with any reasonable degree of predictability. Further, with regards to cultured tumor cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and will not duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Moreover, there is insufficient guidance and objective evidence for one of skill in the art to practice the invention as claimed because the ability to assess the prognosis of a subject who has cancer has not been reasonably quantified with any amount of GLUTx. Furthermore, it has not been shown that GLUTx is a reliable predictor or marker of patient outcome.

Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teaches that prior to the successful application of newly described markers, research must validate these markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and

if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). In addition, Slamon et al. (Science Vol. 235, January 1987, pages 177-182) teach essential factors that are known to be important in the prognosis of breast cancer in individual patients such as size of the primary tumor, stage of the disease at diagnosis, hormonal receptor status, and number of axillary lymph nodes involved with disease (page 178, 1st column, 2nd paragraph). Such data are critical to assessing actuarial curves for relapse (Figure 3), and for comparing disease-free survival and overall survival to prognostic factors (Table 4). In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Rogers *et al.* (WO 99/18125, April 15, 1999).

The claims are drawn to a method for determining whether a subject has a defect in cell proliferation, comprising assaying a diagnostic sample of the subject for GLUTx expression, wherein detection of GLUTx expression elevated above normal is diagnostic of a defect in cell proliferation (Claim 1); wherein the defect in cell proliferation is a neoplasm or a pre-neoplastic lesion (Claim 2); wherein the neoplasm is an adenocarcinoma (Claim 3); wherein the diagnostic sample is assayed using an agent reactive with GLUTx (Claim 4); wherein the agent is labeled with a detectable marker (Claim 5); wherein the agent is an antibody (Claim 6); wherein the antibody is labeled with a detectable marker (Claim 7); wherein the diagnostic sample is assayed using at least one nucleic acid probe which hybridizes to nucleic acid encoding GLUTx (Claim 8); wherein the nucleic acid probe is DNA or RNA (Claim 9); wherein the nucleic acid probe is labeled with a detectable marker (Claim 10).

Rogers *et al.* teach a method for determining whether a subject has a defect in cell proliferation comprising assaying diagnostic samples of patients for GLUT8 expression wherein detection of GLUT8 expression elevated above normal is diagnostic of a defect in cell proliferation. Specifically, Rogers *et al.* teach (page 23) that GLUT8 nucleic acid expression and

protein levels are increased in breast cancer patients versus normal breast tissue using RT-PCR and immunohistochemistry. The use of RT-PCR inherently comprises at least one nucleic acid probe that hybridizes to nucleic acid encoding GLUT8 wherein the nucleic acid probe is labeled with a detectable marker. For immunohistochemical analysis, Rogers *et al.* teach polyclonal antibodies specific for GLUT8 proteins wherein the antibodies are labeled with a detectable marker. It is further noted that Claim 3 is drawn to neoplasms that are adenocarcinomas. The specification teaches (page 7) that "neoplasms include benign tumors and malignant tumors (e.g. carcinomas, including adenocarcinomas such as mammary adenocarcinomas...)". Thus, for the purposes of interpreting the claims, a diagnostic sample of "breast cancer" is equivalent to diagnostic samples of mammary adenocarcinomas. Furthermore, although the reference does not specifically teach "GLUTx", the cited GLUT8 is equivalent to GLUTx since the specification teaches (page 6) that GLUTx also refers to GLUT8.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rogers *et al.* (WO 99/18125, April 15, 1999).

The claims are drawn to a method for assessing the efficacy of therapy to treat a defect in cell proliferation in a subject who has undergone or is undergoing treatment for a defect in cell proliferation, comprising assaying a diagnostic sample of the subject for GLUTx expression, wherein detection of GLUTx expression elevated above normal in the diagnostic sample is indicative of a need to continue therapy to treat the defect in cell proliferation, and normal GLUTx expression in the diagnostic sample is indicative of successful therapy (Claim 11); wherein the defect in cell proliferation is a neoplasm or a pre-neoplastic lesion (Claim 12); wherein the neoplasm is an adenocarcinoma (Claim 13); wherein the diagnostic sample is assayed using an agent reactive with GLUTx (Claim 14); wherein the agent is labeled with a detectable marker (Claim 15); wherein the agent is an antibody (Claim 16); wherein the antibody is labeled with a detectable marker (Claim 17); wherein the diagnostic sample is assayed using at least one nucleic acid probe which hybridizes to nucleic acid encoding GLUTx (Claim 18); wherein the nucleic acid probe is DNA or RNA (Claim 19); wherein the nucleic acid probe is labeled with a detectable marker (Claim 20).

Besides teaching a method of detecting adenocarcinomas in subjects by measuring increased amounts of GLUT8 nucleic acid and protein expression versus normal subjects (see above), Rogers *et al.* further teach a method of monitoring the efficacy of treatment of a

malignant condition comprising the step of detecting activity or expression of GLUT8 in a tissue or cell (page 4, lines 18-21) wherein expression of GLUT8 may be monitored by (see page 6, lines 31+) immunocytochemistry, hybridization analysis, PCR, RT-PCR, and the like, using a sample of tissue or of biological fluid suspected to contain cancer cells. (Also, see page 32 of Rogers *et al.*, i.e. claims 11-12, 16). (GLUTx is equivalent to GLUT8, see above).

Rogers *et al.* do not specifically teach the need to "continue therapy" to treat the defect in cell proliferation when the amount of GLUTx is elevated above normal and/or the indication of successful therapy by normal GLUTx expression in the diagnostic sample.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to "continue therapy" in a subject who has undergone or is undergoing treatment for a defect in cell proliferation or to recognize that said treatment has been successful because Rogers *et al.* specifically teach monitoring the "efficacy" of treatment for a malignant condition comprising the step of detecting activity or expression of GLUT8 in a tissue or cell. One would have been motivated to do so because Rogers *et al.* teach that **high levels** of GLUT8 expression are present in human breast cancer cells versus their normal counterparts (page 23). Since high levels of GLUT8 expression are equivalent to the diagnosis of cancer, the art suggests that it would also be reasonable to monitor such levels during or after therapy. Hence, one of ordinary skill in the art would have a reasonable expectation of success in assessing the efficacy of a therapy to treat a malignant condition because the ability to assess such a therapy is dependent on one variable: GLUT8 expression. Hence, one of ordinary skill in the art would clearly recognize the need to continue therapy if GLUT8 expression was elevated above normal during or following therapy. Conversely, if GLUT8 expression was normal in a subject who has

undergone or is undergoing treatment, it would suggest to one of ordinary skill that such a treatment is successful.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
January 8, 2003